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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/202,054
Filing Date: December 07, 1998
Appellant(s): GODDARD ET AL.

William J. Wood
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/21/2007 appealing from the Office action mailed 11/25/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO91/09614	RUGGERI	7/11/91
5,256,766	COUGHLIN	10/26/93
4,946,778	LADNER	8/7/90

M. Jurk et al., "Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848", Nature Immunology 3:499, 2002.

Rock et al., PNAS 95:588-593.

"Exhibit C" submitted by appellants in the response filed 12/9/2003.

X. Du et al., "Three Novel mammalian toll-like receptors: gene structure expression, and evolution," Eur. Cytokine Netw., 11 (3:)362-71 September 2000.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 28-30, 48-50 and 54-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

At page 3 of the response, applicants argue that the specification teaches that PRO285 polypeptide signaling activates NF-P9 and that antibodies to PRO285 can be used to modulate this activity. This argument has been fully considered but is not deemed persuasive because without knowing under what conditions PRO285 so signals, the use of such antibodies would merely constitute further research to determine the function and biological role of PRO285, which is not considered to constitute a utility under 35 U.S.C. §101. Applicants have submitted with their response a paper by Jurk et al., (Nature Immunology 3:499, 2002), which demonstrates that even four years after the filing date of the instant application, the biological function of PRO285, by applicants assertion later designated TLR7, was unknown. Specifically, Jurk et al. teach that different TLRs signal in response to different stimuli; TLR2, 4 and 5 in response to

peptidoglycan, lipopolysaccharide and flagellin, respectively, TLR6 in conjunction with TLR2 in response to lipoproteins from mycoplasma, TLR9 in response to bacterial DNA containing unmethylated CpG motifs, and TLR3 in response to dsRNA (see abstract). The Jurk paper goes on to state that "The natural ligands for TLR1, TLR7, TLR8 and TLR10 are not known, although a synthetic compound with antiviral activity has not been described as a ligand for TLR7. Thus, even four years after the filing date of the instant application, the role of TLR7, aka PRO285, was unknown, and the receptor was merely a subject for further research. This paper supports the Examiner's position that even *if* one were to accept, on the basis of the specification as originally filed, that PRO285 signals via NF-Kβ, that such does not confer any specific, substantial and credible utility upon the protein, nor upon antibodies that bind to it.

The claims are drawn to antibodies that specifically bind to the protein identified as PRO 285, which may block recognition of a Gram-negative or Gram-positive organism by PRO 285 (as recited in claim 30). The specification discloses that the present invention provides newly identified and isolated human Toll polypeptides and antibodies thereto, and that the Toll polypeptides shows significant homology to proteins that have been identified as human toll-like receptors (it is noted that Toll polypeptide and Toll receptor are used interchangeably in the specification). At page 16 it is asserted that the proteins "may be involved in inflammation, septic shock and response to pathogens, and play possible roles in diverse medical conditions...such as, for example, diabetes, ALS, cancer, rheumatoid arthritis, and ulcers. The role of PRO285, PRO286 and PRO385 as pathogen pattern recognition receptors, sensing the presence of conserved molecular structures present on microbes, is further supported by the data disclosed in the present application, showing that a known human Toll-like receptor, TLR2, is a direct mediator of LPS signaling." Thus, the specification asserts that the claimed antibodies have diagnostic use, and further that they can be used to interfere with binding of PRO285 to bacterial cells. At page 36 the specification further asserts the use of the antibodies for diagnostic assays, and at page 37 line 2, for purification of PTO285.

While the asserted utilities with respect to preventing bacterial binding or use in diagnosis are specific, they would not be considered to be substantial by the skilled artisan. These utilities are predicted based upon predicted properties of anti-TLR2 antibodies, on the basis that PRO285 shares (an unspecified amount) of homology with TLR2. This is not a

substantial assertion of utility. The assertion that anti-PRO285 antibodies can be used for the same purposes as anti-TLR2 antibodies would not be considered substantial by one of skill in the art because such utilities have not been established for TLR2, nor, even if they were, would such be predictive of homologous proteins such as PRO285. It is noted that when the sequence of PRO285 was searched against all available databases, that *no significant homology to TLR2 was detected.* Therefore, it would not be predictable that the two proteins, and hence antibodies that bind such, would share any specific structure or function. There is no disclosure of any disease with which PRO285 itself is correlated, nor any bacterium to which it binds. Finally, use of the claimed antibodies for isolation of PRO285 polypeptides, while specific, is not substantial, as any antibody may be used to isolate its cognate antigen; to confer utility to the antibody, the protein has to have utility. In this case, the only reason for binding PRO285 is for the purpose of learning more about the protein itself, that is, for further research into the properties and characteristics of the protein, which is insufficient to meet the requirement of 35 U.S.C. § 101.

The Examiner's position is supported by art published subsequent to the effective filing date, specifically the Jurk paper. Jurk et al. teach that different TLRs signal in response to different stimuli; TLR2, 4 and 5 in response to peptidoglycan, lipopolysaccharide and flagellin, respectively, TLR6 in conjunction with TLR2 in response to lipoproteins from mycoplasma, TLR9 in response to bacterial DNA containing unmethylated CpG motifs, and TLR3 in response to dsRNA (see abstract). The Jurk paper goes on to state that "The natural ligands for TLR1, TLR7, TLR8 and TLR10 are not known, although a synthetic compound with antiviral activity has not been described as a ligand for TLR7. Thus, even four years after the filing date of the instant application, the role of TLR7, *aka* PRO285, was unknown, and the receptor was merely a subject for further research. This paper supports the Examiner's position that there is no specific, substantial and credible utility upon the protein, nor upon antibodies that bind to it.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentech, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing

> out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification provides the sequence of a protein, and then goes on to invite the reader to find out what the biological significance of the protein is, with suggestions as to what 'might' be. There is no substantial correlation of the protein with any real world, available use, nor, by extension is there any real world use for the claimed antibodies. The instant specification lacks utility and is not enabling because one cannot, following the guidance presented therein, practice the suggested method without first making a substantial inventive contribution.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30, 48-50 and 54-57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruggeri et al., WO 91/09614.

Ruggeri et al. disclose a 19 residue peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 match; see the third peptide listed in claim 1. At page 29 and in claim 65, antibodies to such peptides are disclosed and claimed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggeri et al., WO 91/09614, in view of Coughlin, U.S. Patent Number 5,256,766.

The claims differ from those rejected under 35 U.S.C. § 102(b) above in that they recite that the antibody is a monoclonal antibody.

The teachings of Ruggeri et al. are summarized above. Ruggeri et al. do not teach monoclonal antibodies.

The production of monoclonal antibodies and cells that make them is notoriously old in the art. For example, Coughlin teaches recombinant thrombin receptor and antibodies thereto. Columns 11-12 teach the production of polyclonal and monoclonal antibodies, including hybridoma cells producing the monoclonal antibodies. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make hybridoma cells and monoclonal antibodies as taught by Coughlin reactive with the peptide of Ruggeri. The person

of ordinary skill in the art would have been motivated to do so to attain the known and expected advantages of monoclonal antibodies, viz. ease of production and purification.

Claim 50 and 54 rejected under 35 U.S.C. 103(a) as being unpatentable over Ruggeri et al., WO 91/09614, in view of Coughlin, U.S. Patent Number 5,256,766, and further in view of U.S. Patent Number 4,946,778 (Ladner et al.) .

Ladner et al. teach the construction of single chain antibodies. The stated advantages of such single chain antibodies as enumerated at column 3 lines 32-48 include smaller size, greater stability, lower cost, lower immunogenicity, etc.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make monoclonal antibodies as taught by Coughlin et al. to the peptides of Ruggeri et al., and then generate single chain antibodies as taught by Ladner et al. to attain the known and expected advantages of such as set forth by the secondary reference and as referred to above. It is noted that a single chain antibody is considered to meet the limitation of being a 'chimeric antibody', as claimed in claim 50.

(10) Response to Argument

Appellants have presented their arguments in an order different from that used by the Examiner in making the rejections. For the convenience of the Board, the Examiner will address the arguments in the order presented by appellants.

(A) At page 4 of the appeal brief, Appellants argue that the three dimensional antigenic determinant of the 19 residue platelet membrane glycoprotein Ib peptide is not necessarily present in PRO285. This argument has been fully considered but is not deemed persuasive because according to "Exhibit C" submitted by appellants in the response filed 12/9/2003,

although antibodies raised against fragments generally have higher affinities for the fragment to which they were raised than to the native protein, (page 247) they nonetheless "show extensive cross-reactions with native proteins" (page 248). Further, at page 249, the reference goes on to state that "antipeptide antibodies have proved to be very powerful reagents", and can be used to immunoprecipitate previously unisolated native proteins, to isolate previously unidentified gene products of new genes, and in detecting post-translational processing, are useful in probing structure-function relationships, and can be used to block protein binding. Accordingly, the reference provided by applicants teaches that one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285, and that antibodies to such peptides are well-known as being useful in the art for their ability to bind the full-length protein from which they are derived. Since the Office does not have the facilities for examining and comparing applicants' antibodies with those of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

At page 5, appellants argue that Ruggieri fails to provide a disclosure that allows one to determine whether antibodies raised against the platelet membrane glycoprotein Ib polypeptide will bind to a "completely different protein". This argument has been fully considered but is not deemed persuasive because PRO285 is *not* a "completely different protein", but rather shares 9 contiguous amino acids of a 19-residue long polypeptide. There is evidence of record, "Exhibit C" submitted by appellants, that shows that the person of ordinary skill in the art would expect antibodies to Ruggieri's peptide to bind to PRO285. Applicants have provided no fact or evidence to the contrary.

Also at page 5 of the brief, appellants argue that it is "technically uncertain" that antibodies to Ruggeri's peptide would bind to PRO285, due to the fact that PRO285 is much longer than Ruggeri's peptide, that the residues flanking the 9 amino acids of identity have different chemical properties, and concludes that the difference "provides evidence" that antibodies generiated using Ruggeri's peptide "will not cross-react with the PRO285 polypeptides recited in the claims." The argument concludes with additional speculation by the

attorney, identified therein as speculation and conjecture. This argument has been fully considered but is not deemed persuasive because there is evidence of record, "Exhibit C" submitted by applicants in a previous response, that shows that the person of ordinary skill in the art would expect antibodies to Ruggieri's peptide to bind to PRO285. Applicants have provided no fact or evidence to the contrary. The attorneys speculation and conjecture does not substitute for the facts and evidence that would be required to overcome the *prima facie* finding. Further, there is no fact or evidence of record, nor could the Examiner find any in the art, to support appellants assertions that the flanking residues in the 19 amino acid peptide would be able to distort the conformation of the 9 identical amino acids so as to prohibit generation of the claimed antibodies. As clearly identified by the attorney, such is merely conjecture. It remains that it is well known in the art to raise antibodies to such peptides as disclosed by Ruggeri, and as taught by Ruggeri, and that among those antibodies, one would expect antibodies within the metes and bounds of the claims. Note that although the claims state that the claimed antibodies are "isolated", it is well established in the law that this merely connotes removal from the natural source; it does *not* preclude the presence of other antibodies. Thus, although one might, by raising antibodies to Ruggeri's peptide also obtain antibodies that do not bind PRO285, the evidence of record clearly indicates that at least some of the antibodies so obtained *would* bind to PRO285.

At page 6, appellants argue that the finding of anticipation by Ruggeri is incorrect, as it fails to teach each and every element set forth in the claim, citing *Ex parte Standish, and Verdegall bros. V. Union Oil* in support of the position. This argument has been fully considered but is not deemed persuasive because it remains that Ruggeri et al. disclose a 19 residue peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 match; see the third peptide listed in claim 1. At page 29 and in claim 65, antibodies to such peptides are disclosed and claimed. Since there is a string of 9 amino acids' identity, the antibodies of Ruggeri would be expected to bind PRO285. The sole evidence of record indicates that it would be more likely than not that antibodies to that peptide would meet the claim limitations. Ruggieri places those antibodies in the hands of the public. It is undisputed that disclosing a 19-mer and the desirability of making antibodies to such fairly places such antibodies in the hands of the public. . There is no limitation in the claims that the claimed antibodies be free of any other antibody, nor is there any

limitation that the claimed antibodies be able to bind other regions of PRO285. Thus, all claim limitations are met. The burden has been properly shifted to applicants to show, using *facts or evidence*, that the inherent properties are *not* possessed by the antibodies disclosed by Ruggieri .

The Examienr maintains that the relevant case law is *not* directed to whether or not all the limitations have been taught, since it is maintained that they are, but rather is directed to the burden placed on appellant by the *prima facie* finding of anticipation. Since the Office does not have the facilities for examining and comparing appellants antibodies with those of the prior art, the burden is on appellant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Appellants have not provided any evidence of record that antibodies raised to Ruggeri's peptide do not bind to PRO285. All appellants have provided is evidence (the aforementioned "Exhibit C") that supports the Examiner's assertion that one would expect antibodies to Ruggeri's peptide to bind PRO285 along with speculation and conjecture, as characterized in the appeal brief at the paragraph bridging pages 5-6. Such speculation and conjecture does not meet the burden to show a novel or unobvious difference between the claimed product and the product of the prior art.

At page 6, second and third paragraphs, appellants allege that the Examiner has used conjecture in making the rejection, and that such conjecture is prohibited under 35 U.S.C. §102. Appellants point out that "to establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference'". This argument has been fully considered but is not deemed persuasive because there is no missing descriptive matter. Ruggeri describes a peptide with 9 amino acids identity to PRO285, out of a total of 19 amino acids. Ruggeri describes antibodies to the peptide at page 29, and claims them in claim 65. Accordingly, there is no missing descriptive matter. With regard to the finding of inherency, that Ruggeri's antibodies would be expected to bind to PRO285, the art, as supplied by appellants in the aforementioned "Exhibit C" indicates that the property would be expected to be there, i.e. it would naturally flow from making the antibodies disclosed by Ruggeri. The Examiner notes the decision in *in re Swinehart and Sfiligoj* (169 USPQ 226), which states:

"Mere recitation of newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art; additionally," where the Patent Office has reason to believe that the functional limitation may be inherent, it may require applicant to prove otherwise. In this case, the art of record leads to the expectation that Ruggeri's antibodies would meet the claim limitations. The discovery that Ruggeri's antibodies would bind to PRO285 does not render the antibodies newly patentable. Appellants have not, as suggested in *Swinehart*, provided any evidence to prove otherwise. See also *In re Graves*, 36 USPQ 2d1697 at 1701, where it was held that a reference anticipates a claim if it discloses the claimed invention "such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention" The Examiner maintains that the disclosure of Ruggeri fairly places the invention in the hand of the skilled artisan.

(B) At page 7 of the brief, appellants argue that the remaining art rejections rise or fall with the first; all argument pertains to the Ruggeri reference, which has been fully addressed above.

(C) Beginning at page 7 of the brief, appellants argue the rejection of claims as lacking utility and being non-enabled under 35 U.S.C. §101 and 112, first paragraph.

At page 8 of the brief, appellants argue that the specification teaches that PRO285 polypeptide signaling activates NF-Kβ and that antibodies to PRO285 can be used to modulate this activity. This argument has been fully considered but is not deemed persuasive because without knowing under what conditions PRO285 so signals, the use of such antibodies would merely constitute further research to determine the function and biological role of PRO285, which is not considered to constitute a utility under 35 U.S.C. §101. Appellants, during prosecution, submitted a paper by Jurk et al., (Nature Immunology 3:499, 2002), which demonstrates that even four years after the filing date of the instant application, the biological function of PRO285, by applicants assertion later designated TLR7, was unknown. Specifically, Jurk et al. teach that different TLRs signal in response to different stimuli; TLR2, 4 and 5 in response to peptidoglycan, lipopolysaccharide and flagellin, respectively, TLR6 in conjunction

with TLR2 in response to lipoproteins from mycoplasma, TLR9 in response to bacterial DNA containing unmethylated CpG motifs, and TLR3 in response to dsRNA (see abstract). The Jurk paper goes on to state that "The natural ligands for TLR1, TLR7, TLR8 and TLR10 are not known, although a synthetic compound with antiviral activity has not been described as a ligand for TLR7. Thus, even four years after the filing date of the instant application, the role of TLR7, aka PRO285, was unknown, and the receptor was merely a subject for further research. This paper supports the Examiner's position that even *if* one were to accept, on the basis of the specification as originally filed, that PRO285 signals via NF-Kβ, that such does not confer any specific, substantial and credible utility upon the protein, nor upon antibodies that bind to it.

Appellants specifically assert at page 8 that "antagonistic anti-PRO285 antibodies may be used in pathologies characterized by an overexpression of IL-1, IL-6 and IL-8, such as septic shock." This argument has been fully considered but is not deemed persuasive because it is untrue. While it may be true that reducing those cytokines would be a treatment for effective shock, doing so by administration of anti-PRO285 antibodies would *only* be effective *if* PRO285 had been involved in the induction of those cytokines in septic shock, which is not reported, and in view of the Jurk reference, exceedingly unlikely. As admitted in appellants arguments, there are numerous proteins that may induce pro-inflammatory cytokines. Unless PRO285 is the one responsible for such induction in septic shock, an assertion for which there is absolutely no support, then inhibiting PRO285 would have not effect. At the very best, this would be an invitation to substantial further experimentation. However, considering the Jurk reference, such experimentation would be unlikely to be fruitful.

Also at page 8, appellants assert that "reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts." Appellants cite in the footnote a paper by Beutner to support this position. Presumably, appellants are arguing that this would confer utility to the protein, and therefore the claimed antibodies. With respect to the Beutner article, this argument has been fully considered but is not deemed persuasive because it is not clear to what treatment appellants are referring, as the article in question is a review of numerous treatment modalities for the treatment of genital warts, and the terms IL-1, IL-6 IL-8 and, do not appear in any portion of the article. This argument was set forth in the Office Action mailed 10/26/2004. Appellants failed to further address the issue until this time, and have not at any

time pointed out any specific agent discussed by Beutler that has the asserted function of inducing IL-1, IL-6 or IL-8. Beutner discusses treatment with interferons α and γ, two cytokines that signal through JAK/STAT pathways, and not via NF-Kβ. Further, it was not known or predictable at the time the invention was made that PRO285 would cause NF-Kβ activation, and it is not known what other effects stimulation of PRO285 would have, such that the net effect of such stimulation is unknown. At the very best, this, too constitutes an invitation to experiment to determine the properties of PRO285 and antibodies thereto. . The involvement of IL-1, -6 or -8 in the formation of warts, or in septic shock, is not predictive of the involvement of PRO285 in the same conditions.

At the paragraph bridging pages 8-9, appellants argue that "the use of an antibody to modulate the signalling of a receptor whose biological activity is associated with a pathological syndrome conforms to established scientific principles and is the principle upon which a significant number of therapeutic regimens are based." The Examiner takes no issue with this assertion. However, there has been no association between the signaling of the PRO285 receptor *per se* and any pathological syndrome. Numerous receptors may signal via common pathways; however, different sets of such receptors will be involved in different pathologies. The mere assertion that because appellants believe that PRO285 *may* signal through NF-Kβ does *not* indicate the involvement of PRO285 or its receptor in *any* pathological condition; such remains to be discovered. The Examiner maintains that such discovery constitutes part of the inventive process, and that utility is lacking.

At page 9, appellants state that credibility (substantial nature?) of the assertion of utlity has been established by the filing of the Bazan declaration. The Bazan declaration was fully considered in the Office Action mailed 3/15/2004, to whit:

> "The Bazan declaration filed 12/9/2003 under 37 CFR 1.132 is insufficient to overcome the rejection of claims 28-30, 48-50 and 54 35 U.S.C. §101 and §112 as set forth in the last Office action because:
>
> Dr. Bazan refers to the specification at Figure 7B and page 7, lines 8-23 as showing that PRO285 has significant homology to the IL-1 receptor domain that is necessary for signaling via NF-Kβ and that such would be predictive of NF-Kβ -

mediated signaling by PRO285. This argument has been fully considered but is not deemed persuasive because Figure 7 shows an alignment of IL-1R with TLR2 in the region critical for IL-1R signaling. However, examination of Figure 7B reveals that six residues are indicated as being "essential for IL-1R signaling", and only three of those six are conserved in TLR2, which had not, as of the filing date of this application, been shown to signal via NF-Kβ. The declaration provides, for the first time, an alignment of the analogous region of PRO285 with both IL-1R and TLR2. The Examiner notes that of the *six essential residues* for IL-1R signaling, only *two* are conserved in PRO285. This amount of conservation is not persuasive of conservation of function. Therefore, based upon the information in the specification as originally filed, it does not appear that it would lead a person of ordinary skill in the art to the conclusion that PRO285 would be expected to have NF-Kβ signaling activity.

At paragraphs 6-7, Dr. Bazan refers to an article by Rock et al., PNAS 95:588-593, previously of record, as teaching that it would be expected that PRO285 would signal via NF-Kβ. This argument has been fully considered but is not deemed persuasive because while the Rock article clearly shows that five TLRs were evolutionarily related to the *Drosophila* Toll receptors, there is no clear indication that they would be expected to activate NF-Kβ, nor is there disclosure or discussion of PRO285. Declarant is arguing based on two steps removed from the data; the argument is that the function of IL-1R was known, that TLRs are similar to IL-1R and thus might share function, and that PRO285 is similar to TLRs. Further, mere signaling via NF-Kβ would not be indicative of utility, for reasons cited below. While the Rock et al. paper states that the TLRs "could constitute an important and unrecognized component of innate immunity in humans", it also states, in the very next sentence, that "Intriguingly, the evolutionary retention of TLRs in vertebrates may indicate another role- akin to Toll in the dorsoventralization of the *Drosophila* embryo- as regulators of early morphogenetic patterning. Finally, the Rock paper does not disclose or discuss PRO285. Thus, based upon the Rock paper, it would seem that it was *not* predictable that PRO285 was involved in innate immunity via signaling via NF-Kβ, and that there were at least

two very distinct ideas as to what the receptors disclosed therein might do. Finally, the fact that TLR4 was confirmed as signaling via NF-Kβ does not have bearing on PRO285.

At paragraph 8, Dr. Bazan concludes that the person of ordinary skill in the art could, reading the specification, reasonably conclude that PRO285 signals via NF-Kβ, and that "antibodies to PRO285 could be made and used in accordance with routine techniques to modulate such activity." This argument has been fully considered but is not deemed persuasive because it is the opinion of the declarant, and is not supported by the facts and evidence of record, specifically: (a) As stated above, as essential residues of the IL-1R signaling domain are *not* conserved in PRO285, the Examiner does not agree with the assertion that the person of ordinary skill in the art, reading the specification as originally filed, would find it predictable that PRO285 signals via NF-Kβ. (b) The Rock publication indicates that TLRs *might* signal via NF-Kβ, or alternatively, *might* be involved in early morphogenic patterning, and does not disclose or discuss PRO285. (c) Even *if* it were predictable that PRO285 signaled via NF-Kβ, such is not a utility, in and of itself. NF-Kβ is an intracellular signaling molecule. Without knowing any ligand for PRO285 nor under what physiological circumstances the ligand binds to the receptor, the person of ordinary skill in the art would not know how to use the receptor for its NF-Kβ signaling activity, that is, under what circumstances it would be desirable to stimulate or inhibit PRO285."

Appellants argument at the bottom of page 9 that conservative substitutions must be considered when deciding whether the replacement of four of the six *essential* cysteine residues is significant has been fully considered but is not deemed persuasive. Cysteine residues are different than *all* other amino acids, by virtue of their ability to form disulphide bonds, wherein one cysteine is linked to another. This property of disulphide bonding is very important to the ability of proteins to assume the proper secondary structure necessary for function. No other amino acid can do this. Therefore, there is no additional homology consideration. If four of the six *essential* cysteine residues are missing, it would be expected that the function of the protein would be different. Appellants additionally refer in this regard to an amendment filed 12/9/2003; the Examiner can find no discussion of this particular issue therein. Appellants also refer to

pages 5-6 of the amendment filed 7/15/2004; once again, the Examiner finds no assertion therein to the effect that replacing four of six essential cysteine residues would not be expected to significantly change the properties of the protein.

At page 10 of the brief, appellant argues that "As noted in M.P.E.P. §2107.02, where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong" even when there may be reason to believe that an assertion is not entirely accurate. Instead, an assertion of utility is to be considered credible unless (A) the logic underlying the assertion is seriously flawed, or B) the facts upon which re assertion is based is inconsistent with the logic underlying the assertion." The Examiner concurs. In this case, appellants assert that PRO285 signals via the NF-Kβ pathway, and that this confers utility and enablement on the claimed antibodies. The specification also asserts that PRO285 should have function similar to other toll-like receptors on the basis of sequence similarity, and that the antibodies can be used to interfere with binding of PRO285 to bacterial cells. However, both conditions A and B as quoted from the MPEP by appellants have been met: the logic underlying the assertion is seriously flawed, and the facts are inconsistent with the logic underlying the assertion because there is no significant homology to TLR2 (contrary to applicants assertion), there is no basis for the assertion that replacement of four out of six *essential* cysteine residues is unimportant, there not only is no evidence that PRO285 binds bacterial cells, but rather, to the contrary, the art four years after the filing date states that no receptor for PRO285 had yet been identified, there are no known diseases or conditions associated with PRO285, antibodies to PRO285 would not be useful to interfere with production of IL-1, 6, or 8 *unless* such production were induced by PRO285, which is neither predictable nor shown, and hence, contrary to appellants assertion at page 10, there is no reasonable correlation between the activity and the asserted use.

Finally, the Examiner notes the disclosure of Du et al., cited by appellants in making a previous argument. Though not reiterated in the appeal brief, appellants have previously argued that that isolation of Toll homologues on the basis of homology is practiced in the art, and that "functional data relating to one Toll family member such as TLR2 can reasonably suggest functions of other Toll homologues", citing a paper by Du et al., published after the filing date of this application, in support of their argument. This argument has been fully considered but is

not deemed persuasive because Du does not support that assertion. The person of ordinary skill in the art would *not* accept an assignment of function based upon mere membership in the Toll family of proteins. To quote Du et al. at page 369:

> "The assignment of function to distinct members of the Tlr family is of paramount importance in this rapidly developing field. *We are able to draw no substantial inferences based on the distribution of TLR gene expression.*" (Emphasis added.) Continuing in the same paragraph, "The function of Tlr4 as an LPS receptor has been demonstrated by the identification of two naturally occurring mutations that render mice resistant to LPS, and subsequently was confirmed by knockout of the gene."

Thus, Du et al. teach that sequence homology and expression information are *not* considered predictive of function by the person of ordinary skill in the art, and that substantial further experimentation, such as obtaining animals with specific mutations or knock-outs of the gene in question are the type of investigation that must be done to establish a specific function for a newly identified gene such as PRO285, which is asserted to be a new member of the TLR family. Thus, the Examiner maintains that mere assertion that PRO285 is a member of the Toll family is not sufficient to support any of the asserted utilities as being substantial.

It is believed that all pertinent arguments have been addressed. It is noted that all separate argument of the rejection under 35 U.S.C. §112, first paragraph is by reference to the arguments addressed above. It is believed that the rejection under 35 U.S.C. §101 is proper, and properly supports the rejection for lack of enablement. However, should the Board find that the assertions meet the requirements of 35 U.S.C. §101, the Examiner urges the Board to consider also whether the disclosure is enabling under 35 U.S.C. §112, first paragraph, on the basis of the same grounds and reasoning as set forth herein. The enablement rejection has been made in association with the rejection under 35 U.S.C. §101. However, it is well established that the bar for enablement is higher than that for utility, and the Examiner believes that the rejection sets for a clear case that the invention is *also* not enabled, based upon the teachings in the specification which are assertions based upon faulty assumptions (such as that the homology between PRO285 and TLR2 is "significant"), the lack of any working example in which PRO285 is shown to have the asserted function of signaling via NF-Kβ, the lack of association between PRO285 and any

disease or condition, the lack of teaching in the art that the mere finding that a protein that signals via NF-Kβ (if indeed PRO285 does so) confers an enabled use on the protein, the teaching in the art by by Jurk et al., (Nature Immunology 3:499, 2002), which demonstrates that even four years after the filing date of the instant application, the biological function of PRO285, by applicants assertion later designated TLR7, was unknown (the fact that persons in the art have been attempting to assign a function to the protein without avail is particularly significant and supports the finding that undue experimentation would be required), the finding that despite appellants assertion that PRO285 has "homology" to TLR2, that *no significant homology to TLR2 was detected* when the sequence was searched by the Examiner (and no further clarification offered by appellants as to the perceived "homology"), leading to the requirement for undue experimentation to determine what the properties of PRO285 are, and how to turn such into a use within the meaning of 35 U.S.C. §112, first paragraph.

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Argument

Should appellants request an oral hearing, the Examiner respectfully requests to be present to present arguments.

Respectfully submitted,

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